ents of blood products were different. The studies taken as a group, however, suggest that the exclusive use of volunteer blood may be the most useful measure to prevent posttransfusion hepatitis. Others have shown that serum alanine aminotransferase (ALT) or anti-hepatitis B core antibody (anti-HBc) testing of blood donors and rejection of blood units with elevated ALT or anti-HBc levels may decrease the incidence of posttransfusion hepatitis in recipients. Whether or not immune globulin administration or any other measure can reduce the incidence of hepatitis after transfusion of volunteer blood with normal ALT levels and absent anti-HBc remains to be proved. To date, blood banks have not adopted a policy of screening for these serologic markers epidemiologically associated with non-A, non-B hepatitis infectivity. A recent randomized, placebo-controlled trial of HBIG versus placebo in hemodialysis patients has shown prevention of non-A, non-B hepatitis during but not after administration of HBIG, suggesting that protection was passive and no active immunization occurred.

Treatment studies in this illness continue to be hampered by the lack of reliable diagnostic tests. An unknown number of cases of posttransfusion non-A, non-B hepatitis have been included in trials of corticosteroids in treating chronic active hepatitis. The proper management of chronic active non-A, non-B hepatitis may include a trial of prednisone if the illness is symptomatic, serum aminotransferase and globulin levels are moderately to greatly elevated and a liver biopsy specimen shows severe active liver disease. At Stanford University Medical Center we are currently enrolling patients in a pilot study of human leukocyte interferon for treating patients with posttransfusion non-A, non-B chronic active hepatitis.

Identifying the agent of non-A, non-B hepatitis and developing reliable diagnostic laboratory tests for its detection will allow rigorous reexamination of the data summarized above. A better understanding of the natural history and transmissibility of non-A, non-B hepatitis will then allow a rational approach to its treatment and prevention.

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New Antibiotics

SEVERAL NEW ANTIBIOTICS entered into clinical practice in 1984 and the role of the third-generation cephalosporins was better defined. Although the latter antibiotics are costly, they have several advantages over first- or second-generation cephalosporins and a very competitive race has ensued between cefotaxime, moxalactam, ceftizoxime, ceftazidime and cefoperazone. These agents are frequently used in the empiric treatment of patients with infections like bacterial sepsis, bacillary meningitis or pneumonia before the cause is identified by laboratory studies. Physicians often substitute these compounds for aminoglycosides such as tobramycin and gentamicin to avoid nephrotoxicity. This is particularly the case in infections such as septicemia and community-acquired pneumonia in immunocompromised patients.

Another new antibiotic is a combination of clavulanic acid with ampicillin. The former compound binds β-lactamases of Gram-positive and Gram-negative bacteria, thus allowing ampicillin to penetrate bacterial cells before it is destroyed. Organisms frequently resistant to ampicillin such as *Staphylococcus aureus, Klebsiella* and other Gram-negative bacilli are now sensitive. This compound is taken orally and can be used in treating complicated outpatient infections. We are also looking with interest at a new class of antibiotics known as the quinolines (pyridonecarboxylic acid compounds) which are derived from nalidixic acid. Such agents include ciprofloxacin, norfloxacin and enoxacin and have a broad range of antibacterial activity against both Gram-positive and Gram-negative bacteria. The bottom line is that a physician who practices primarily in the outpatient arena will have several new compounds effective against complicated infections and that will shorten hospital stays.

The concept of diagnosis-related groups (DRGs) and its inherent logic that dictates reimbursing hospitals is also having an effect on antibiotic prescriptions. Hospitals are looking to their pharmacies to provide tighter guidelines for the use of antibiotics, as they often account for 20% to 30% of all pharmacy purchase costs. New ways are also being developed to treat morbid infections in the outpatient clinical area and thus decrease the duration of hospital stay for patients who have resolving infections such as osteomyelitis, abdominal abscess, pneumonia, empyema and even endocarditis. Infusion centers exist where patients can receive on a daily outpatient basis antibiotics via Hickman lines or catheters in peripheral veins with "heparin locks." Another approach is to employ nurses to visit the homes of patients to administer antibiotics daily. Antibiotic costs will probably gain in importance as a deciding factor in their use.

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Calcium Channel Blockers

CALCIUM CHANNEL BLOCKING agents are important new drugs used in treating coronary and other cardiac diseases. The currently available drugs, diltiazem hydrochloride, nifedipine and verapamil, have been effective in treating coronary artery spasm, and their use in the management of angina and supraventricular arrhythmias has been well documented. The ability of these agents to prevent or relieve spasm theoret-

ically makes them ideal for use in treating other smooth muscle disorders. Although the three available drugs all inhibit the entrance of calcium into cells, they are different compounds and vary in their clinical effect. Nifedipine is a stronger peripheral vasodilator, verapamil causes more myocardial depression and diltiazem and verapamil affect the sinoatrial and atrioventricular nodes. Consideration of these factors is important in choosing which drug will be used, either alone or combined with other drugs such as β-blockers or nitrates.

Several clinical trials have shown the effectiveness of these drugs in treating systemic hypertension, often used as monotherapy. Nifedipine has been extensively studied and may be more beneficial due to its more potent peripheral vasodilating property, and it is very effective in managing cases of hypertensive crisis. Verapamil and diltiazem are also effective in treating hypertension and it is felt by some that they may be more suitable for long-term treatment because nifedipine is more likely to lead to reflex activation of the sympathetic nervous system.

The use of calcium channel blocking drugs in the treatment of pulmonary hypertension is encouraging. All three drugs have reduced pulmonary artery pressure and pulmonary vascular resistance in patients with primary pulmonary hypertension and some types of secondary pulmonary hypertension. However, the response to calcium entry blocking agents in patients with precapillary pulmonary hypertension is unpredictable and the drugs may sometimes produce deleterious effects.

Active clinical investigation is continuing in the use of calcium channel blockers for other conditions, including congestive heart failure, hypertrophic cardiomyopathy, myocardial preservation, bronchial asthma, Raynaud's phenomenon, migraine headache, cerebrovascular spasm, cerebral ischemia, premature labor and disorders of esophageal motility. Calcium channel blockers will likely be increasingly used in smooth muscle disorders, especially as new drugs become available that are more specific for certain types of smooth muscle.

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The Protein C Anticoagulant Pathway and Thrombosis

PROTEINS C AND S are recently discovered vitamin K-dependent proteins that unlike the other vitamin K-dependent clotting factors—II, VII, IX and X—act as physiologic anticoagulants rather than procoagulants. Activated protein C inhibits coagulation by destroying activated factors V and VIII; protein S is an essential cofactor in the expression of protein C's anticoagulant activity. Protein C circulates in an inactive zymogen form and is activated by thrombin bound to an endothelial-cell surface protein, thrombomodulin. Activated protein C may also have a stimulatory effect on fibrinolysis. The protein C anticoagulant pathway thus provides a mechanism whereby formation of thrombin is accompanied by generation of anticoagulant and profibrinolytic activity, limiting fibrin formation to areas of local vascular damage.

Hereditary deficiencies of the protein C anticoagulant mechanism are associated with venous thromboembolic disease. Heterozygous protein C-deficient persons have about half the normal amount of protein C. Many but not all manifest recurrent episodes of thrombophlebitis, pulmonary embolism or both, beginning after the first decade of life, often associated with a precipitating event such as trauma or an operation. Administering heparin or warfarin is effective. Warfarin therapy reduces the levels of all vitamin K-dependent proteins, but protein C levels fall faster than levels of factors II, IX and X. Therefore initiating warfarin therapy, especially with loading doses, may create a brief period of increased vulnerability to thrombosis, including the rare syndrome of dermal thrombosis with necrosis ("warfarin skin necrosis"). Such complications can be avoided by continuing a regimen of heparin for several days, until full oral anticoagulation has occurred.

Homozygous protein C deficiency has been described in several newborns, who have little or no detectable protein C and who show dramatic, life-threatening thrombotic complications, including purpura fulminans, a necrotic dermal thrombotic lesion closely resembling warfarin skin necrosis. Constant protein C repletion with prothrombin complex concentrate is the only effective therapy so far described; however, this therapy is associated with a risk of transmitting hepatitis. Acquired deficiency of protein C is seen in cases of disseminated intravascular coagulation, liver disease, vitamin K deficiency and warfarin therapy; the clinical consequences of such deficiency states are not well established.

A diagnosis of protein C deficiency is best made with one of the recently described functional assays, as normal levels of a functionally defective molecule will not be detected by antigenic assays. Its diagnosis in a patient receiving warfarin requires finding a disproportionately low protein C level when compared with that of another vitamin K-dependent protein, such as factor II, VII or X.

Partial or complete protein S deficiency causes a tendency to venous thromboembolic disease very similar to that of heterozygous protein C deficiency. The use of warfarin or heparin is effective treatment. Neither protein C nor protein S deficiency has been clearly shown to increase the risk of arterial thromboembolism. A search for other defects in the protein C anticoagulant pathway, such as quantitative or qualitative deficiencies of thrombomodulin, is under way in many laboratories and may further increase our understanding of the pathophysiology of thromboembolic disease.

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